

### **REMARKS**

Reconsideration of the rejection of all claims is respectfully requested in view of the above amendments and the following remarks.

#### ***Claim Amendments***

Claims 1-9 have been cancelled as being in a "use" format not generally accepted under US practice.

Kit claim 11 has been cancelled for the purpose of reducing the excess independent claims fee.

Method claims 12-13 have been amended to more specifically recite a method for the treatment of cancer. Support for this amendment is found, *inter alia*, at specification page 4, lines 27-31 and page 8, lines 5-10, respectively.

New claim 14, 15 and 16, dependent on amended claims 12 and 13, are directed toward the platinum anti-tumour agent being cisplatin, carboplatin and oxaliplatin, respectively, and find support, *inter alia*, in original claims 7, 8 and 9, respectively.

New claim 17, dependent on amended claims 12 and 13, is more specifically directed toward a method for the treatment of a cancer involving a solid tumour, and finds support, *inter alia*, at specification page 4, line 32 through page 5, line 3, and at specification page 8, lines 11-16.

New claim 18, dependent on claim 17, is more specifically directed toward the solid tumour cancer being a tumour of the colon, pancreas, bladder, breast, prostate, lungs and skin, and finds support, *inter alia*, at specification page 11, lines 22-24.

New claim 19, dependent on claim 18, is more specifically directed toward the tumour being colorectal cancer, and finds support, *inter alia*, at specification page 11, lines 25-27.

New claim 20, dependent on claim 18, is more specifically directed toward the tumour being a lung tumour selected from mesothelioma and non-small cell lung cancer, and finds support, *inter alia*, at specification page 11, lines 25-27.

It should be clear from the above that no new matter has been added by the above amendments, and entry of these amendments is therefore believed to be in order and is

respectfully requested. These amendments are being made without disclaimer or prejudice to Applicants' right to prosecute any subject matter deleted by these amendments in one or more continuing applications.

Following entry of these amendments, claims 10 and 12-20 remain pending in this application.

***Claim Rejections - 35 USC § 112, 2<sup>nd</sup> Paragraph***

Claims 1-9, 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the term "reducing effect" in claims 1, 4, 7-9, 12-13 is said to be a relative term which is asserted to render the claims indefinite. While Applicants do not agree with this ground for rejection, it has become moot my cancellation of claims 1, 4 and 7-9 and the amendment to claims 12 and 13 to more specifically direct them to a method for the treatment of a cancer.

The Examiner further notes that claims 1-6 and 12-13 use the phrase "such as" which renders the claims indefinite. This ground for this rejection has been overcome by the cancellation of claim 1-6 and the deletion of "such as a human" from claims 12 and 13.

The Examiner further rejects claims 1-9 as being indefinite in that they are in a "use" or "Swiss-type" format not generally accepted under US practice. This ground for rejection has been obviated by the cancellation of these claims.

***Claim Rejections - 35 USC § 101***

The rejection of claims 1-9 under 35 U.S.C. 101 as being in a "use" format has also been obviated by the cancellation of these claims.

***Claim Rejections - 35 USC § 103***

The Examiner is thanked for considering "use" claims 1-9 as method claims in order to provide a substantive Action on the patentability of Applicants' invention. Claims 1-9 (and 11) have been cancelled as noted above, but the obviousness grounds for rejection will be

addressed below in context of remaining (and new) claims 10 and 12-20. The Examiner has advanced two combinations of references said to render various of the claims obvious, which grounds will be separately discussed below.

(1) Rejection of Claims 1-6 and 10-13 over Hennequin WO '651 + Kuenen + Gorski

Claims 1-6, 10-13 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Hennequin *et al.*, WO 01/32651 (hereinafter “Hennequin WO '651”) in view of Kuenen *et al.*, Journal of Clinical Oncology (hereinafter “Kuenen”) and Gorski *et al.*, Cancer Research (hereinafter “Gorski”).

ZD6474 is one of the compounds falling within the generic scope of the disclosure of Hennequin WO '651, and the present specification acknowledges at page 3 that ZD6474 is one of the compounds named and exemplified therein. Specifically, ZD6474 is exemplified in Example 2a and is otherwise identified by its chemical name. Hennequin WO '651 discloses at page 28 that compounds defined by the invention disclosed therein are of interest for their antiangiogenic and/or vascular permeability reducing effects and, in particular, are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. The present specification further notes at page 3 that it is stated in Hennequin WO '651 that compounds of their inventions: “may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments,” and that “such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment.”

The Examiner asserts that Hennequin WO '651 “suggests the use of radiotherapy (p 26, line 30) and platinum derivatives (for example cisplatin, carboplatin) in combination with ZD6474 as conjoint treatment in the field of oncology (p 27, lines 24-25).” However, this statement referred to by the Examiner must be considered in the context in which it is made. Thus, while Hennequin WO '651 does list “platinum derivatives (for example cisplatin, carboplatin)” as one of the many chemotherapeutic drugs that might be used in combination with one of the compounds of their invention, this listing is only of part of the overall discussion of such conjoint treatment in Hennequin WO '651 as follows:

The antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be surgery, radiotherapy or chemotherapy. Such chemotherapy may cover five main categories of therapeutic agent:

(i) other antiangiogenic agents that work by different mechanisms from those defined hereinbefore (for example linomide, inhibitors of integrin  $\alpha v \beta 3$  function, angiostatin, endostatin, razoxin, thalidomide) and including vascular targeting agents (for example combretastatin phosphate and the vascular damaging agents described in International Patent Application Publication No. WO 99/02166 the entire disclosure of which document is incorporated herein by reference, (for example N-acetylcolchicol-O-phosphate));

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, idoxifene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide, abarelix), inhibitors of testosterone  $5\alpha$ -dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors);

(iii) biological response modifiers (for example interferon);

(iv) antibodies (for example edrecolomab); and

(v) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin,

mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); enzymes (for example asparaginase); thymidylate synthase inhibitors (for example raltitrexed); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, irinotecan).

For example such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of a compound of formula I as defined hereinbefore such as 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline or a salt thereof especially a hydrochloride salt thereof, and a vascular targeting agent described in WO 99/02166 such as N-acetylcolchicol-O-phosphate (Example 1 of WO 99/02166).

(Hennequin WO '651 at page 26, line 22 through page 28, line 4).

The Examiner thus correctly acknowledges at the top of page 6 of the Action that Hennequin "does not however teach the specific use of ZD6474 with platinum derivatives." However, the Examiner then asserts that "this deficiency is cured by teachings of Kuenen who teaches the use of cisplatin and SU5416 in patients with solid tumors." In making this assertion, the Examiner argues "that SU5416 is also a small molecule VEGF receptor inhibitor similar in its mechanism of action to ZD6474, and that Kuenen additionally teaches the advantages of combining angiogenesis inhibitor with chemotherapy" (citing page 1658, paragraph 2).<sup>1</sup>

Applicants respectfully traverse this assertion, and respectfully submit that Kuenen, when its disclosure is considered as a whole, does not "cure" this deficiency in Hennequin WO '651. If anything, it is believed that the Kuenen reference would *lead away* from the presently claimed combination therapy.

Firstly, this reference relates to a three component combination of Cisplatin + Gemcitabine + SU5416. Specifically, it is reported under the Discussion at page 1663 that the

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<sup>1</sup> It is submitted that this paragraph of Kuenen does "teach the advantages", but rather states that "other theoretical advantages may be foreseen by the combination of chemotherapy with angiogenesis inhibitors." However, as discussed further below, the Kuenen study clearly demonstrated that any such "theoretical advantages" were negated by the high incidence of adverse effects of the combination, as described further below.

study was set up in preparation for a large randomized study in advanced NSCLC, in which chemotherapy with cisplatin/gemcitabine was going to be compared with the same chemotherapy plus SU5416.<sup>2</sup> Thus the starting point of the therapy is a combination of cisplatin and gemcitabine, and the purpose of the study was to test this established chemotherapeutic combination of cisplatin and gemcitabine with and without SU5416 as a third component. There is *no suggestion* of a combined therapy of cisplatin and SU5416 *alone* without gemcitabine, and thus there is certainly no teaching or suggestion that there might be any benefit of a combination of cisplatin with some other inhibitor of VEGF, such as ZD6474, as the Examiner seems to be arguing.

Moreover, the studies of Kuenen observed a high incidence of thromboembolic events (four venous thromboembolic events plus 5 vascular events in 8 of 19 patients), causing the phase I study to be terminated (page 1662, left column). Additionally, Kuenen notes in the paragraph bridging pages 1665 and 1666 a reported study in which carboplatin/paclitaxel was combined with a recombinant humanized monoclonal antibody to VEGF, which resulted in “sudden and life-threatening hemoptysis ... in six (four fatal) of 67 patients with NSCLC stage IIIb/IV treated with this combination.” Kuenen then notes at page 1666 that “these findings, together with our study, suggest an interaction of chemotherapy and biologic against targeting the VEGF/VEGFR pathway with the coagulation cascade, ECs, or both.” The authors therefore decided not to further pursue the continuation of the Kuenen trial. They concluded at page 1666 that “the combination of the VEGFR-2 inhibitor SU5416 with cisplatin/gemcitabine seems not to be safe in patients with advanced solid tumors.”

Therefore, when the Kuenen reference is read as a whole for all of its teachings (as must be done), the reference clearly does not teach or lead the skilled person to the presently claimed invention of a combination therapy with ZD6474 and a platinum anti-tumour agent and, if anything, *leads the skilled person away* from making such a combination.

The Examiner cites Gorski to add in the teaching of a combination with ionizing radiation. Gorski is not cited for curing (and does not cure) the deficiency of Hennequin WO

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<sup>2</sup> “The combination of cisplatin and gemcitabine is a regimen often used for the treatment of several solid tumors, including non-small-cell lung cancer (NSCLC).” Kuenen at page 1658, near top of left column.

'651 discussed above with respect to the platinum anti-tumour agents, and certainly does not overcome the negative teaching of Kuenen.

Gorski is cited for its disclosure of the use of ionising radiation and an anti-VEGF (vascular endothelial growth factor) antibody in a number of mouse xenograft models. The anti-VEGF antibody binds to free VEGF ligand which is then not available to bind to the VEGF receptor. Thus the anti-VEGF antibody does not act as an inhibitor of the VEGF receptor directly. Conversely ZD6474 is a VEGF receptor tyrosine kinase inhibitor that is an anilinoquinazoline namely: 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline. ZD6474 binds to the intracellular tyrosine kinase domain of the VEGF receptor and thus acts at a different point in the VEGF signalling pathway. The profile of activity of ZD6474, being a small molecule tyrosine kinase inhibitor that acts intracellularly will be different to that of a VEGF antibody that binds VEGF extracellularly. Given the different structures, modes of actions and profiles of inhibitory activity of the anti-VEGF antibodies described in Gorski, it is respectfully submitted that this reference would not have given a reasonable expectation that ionising radiation, when combined with a combination therapy of ZD6474 and a platinum anti-tumour agent, would have provided any advantageous result.

Moreover, and again, Gorski does not cure the deficiency of the disclosure of Hennequin WO '651 with respect to the platinum anti-tumour agents in the presently claimed combination therapy, and certainly does not overcome the negative teaching of Kuenen discussed above.

The Examiner has cited *In re Kerkhoven* with respect to claims 10 (pharmaceutical composition) and 11 (a kit, now cancelled), arguing that since both ZD6474 and platinum compounds are known chemotherapeutic agents it would have been *prima facie* obvious to combine them. However, the Court in *In re Kerkhoven* repeatedly notes that this implication of *prima facie* obviousness is appropriate only in the absence of a showing of unexpected results.

It is respectfully submitted that the negative outcome reported with respect to the combination tested in the prior art Kuenen reference would, if anything, lead the skilled

person away from the present combination, and moreover would counter any implied *prima facie* obviousness that might be said to arise from *In re Kerkhoven*.

In addition, it is respectfully submitted that the test data provided in the application itself, as well as test data reported in the two literature references submitted herewith, clearly demonstrate that the claimed combination of ZD6474 and a platinum anti-tumour agent unexpectedly provides a very significantly enhanced, or even synergistic improvement in efficacy in the treatment of cancer.

Thus, the results of the experiment described in the specification, graphically shown in Figure 1, demonstrate the very significantly improved reduction in tumour growth in a human lung cancer (NSCLC) xenograft model by administration of a combination of 4mg/kg cisplatin + 25mg/kg ZD6474 relative to both 4mg/kg cisplatin and 25mg/kg ZD6474 when administered alone.

Confirmation of this unexpected result is provided by the following two further studies, which show a marked synergistic effect of the combination of ZD6474 and platinum agents when the ZD6474 is give after the platinum agent.

*Morelli et al (2005) Annals of Oncology 16(4) iv61-iv68* shows a marked synergy when ZD6474 is give after cisplatin, carboplatin or oxaliplatin. The Examiner's attention is drawn, in particular, to Table 1 of this reference, which reports the effects on KYSE30 cancer cell<sup>3</sup> growth of the various combinations of EGFR inhibitors and cytotoxic drugs. The 4<sup>th</sup> line of this table reports the results for chemotherapy followed by ZD6474 in terms of CI at IC<sub>50</sub>, being 0.08, 0.08 and 0.14 when the chemotherapy is cisplatin, carboplatin and oxaliplatin, respectively. At the very end of the paragraph directly beneath Table 1 it is noted that "CI values less than 0.3 [indicate] strong synergism."

*Troiani et al (2006) Mol. Cancer Then 5(7) 1883-1894* shows that treatment with oxaliplatin followed by ZD6474 was highly synergistic. The Examiner's attention is drawn, in particular, to Figure 2 in this reference, which graphically shows the effect discussed at pages 1886-87 achieved from a combination of ZD6474 and oxaliplatin on colorectal cancer

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<sup>3</sup> Human KYSE30 esophageal squamous epithelial cancer cells (page iv62 under "Cell line), a model of a human cancer cell line with a functional EGFR autocrine pathway (Abstract).



cells.<sup>4</sup> It is reported at page 1886, right column, “[a]s shown in Fig. 2, a 24-hour exposure to oxaliplatin followed by 48-hour exposure to ZD6474 resulted in clear synergy with a CI between 0.2 and 0.5 in both HT29 and HCT-116 cells.”<sup>5</sup>

The Examiner concludes at page 7 of the Action that the above references in combination render claims 1-6 and 10-13 *prima facie* obvious in that one of ordinary skill in the art would have been motivated to make the presently claimed combination and combination therapy “in order to develop a more powerful cancer treatment method than existing ones” with “a reasonable expectation of success since each of the components has been shown to have their own anti-tumor activity”. However, as demonstrated above, the Kuenen reference itself does not support the Examiner’s assertion and would lead one away from combining it with Hennequin WO ‘651. Thus the acknowledged deficiency of Hennequin WO ‘651 with respect to combining ZD6474 with a platinum agent is not cured, nor is it cured by Gorski. Therefore, the asserted combination of references does not give rise to *prima facie* obviousness.

However, even if *prima facie* obviousness is implied from *In re Kirkhoven*, it is respectfully submitted that the above discussion of the references applied by the Examiner and the comparative data presented in Figure 1 of the present application augmented by the comparative tests reported in the Morelli and Troiani publications refute and overcome any such *prima facie* obviousness. Withdrawal of this ground for rejection is therefore respectfully requested.

## (2) Rejection of Claims 7-9 over Hennequin WO ‘651 + Desoize + Gorski

At pages 7 *et seq.* of the Action, claims 7-9 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Hennequin WO ‘651 in view of Desoize et al. (Critical reviews in Oncology/Hematology, vol 42, pp 317-325 (hereinafter “Desoize”) and Gorski. Claims 7-9 are characterized as being drawn to *a use* of ZD6474 combined with platinum anti-tumor

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<sup>4</sup> “Human colon cancer cell lines HCT-116 (p53 mutated; Ras wild-type) and HT29 (p53 wild-type; Ras mutated)” (page 1884, right column).

<sup>5</sup> The report further notes that the reverse sequence and concurrent exposure were both antagonistic.

agent wherein the platinum anti-tumor agent is Cisplatin (claim 7), Carboplatin (claim 8) and Oxaliplatin (claim 9).

It should be noted that “*use*” claims 7-9 have been cancelled by the above amendments, and replaced by new *method of treatment* claims 14, 15 and 16 (dependent of amended claims 12 or 13), wherein the platinum anti-tumour agent (in combination with ZD6474) is cisplatin, carboplatin and oxaliplatin, respectively. Therefore, to the extent that this ground for rejection of claims 7-9 is based on these claims being in a “*use*” format and therefore considered as composition claims, this ground for rejection has been overcome by the cancellation of these *use* claims and their replacement with proper *method of treatment* claims 14-16.

Nevertheless, this ground for rejection will be discussed below in context of new method of treatment claims 14-16, and is respectfully traversed whether applied to now-cancelled use claims 7-9 or new method of treatment claims 14-16.

The Examiner applies Hennequin ‘651 in the same manner as applied in the above-discussed obviousness rejection.

On page 8 of the Action the Examiner acknowledges that Hennequin fails to teach the use of Oxaliplatin with ZD6474, but asserts that this deficiency is cured by teachings of Desoize, who are said to teach “that the mechanism of action of cisplatin, carboplatin and oxaliplatin are similar in that they all are pro-drugs which form adducts with DNA, impairing DNA synthesis and repair (Abstract, Page 317), page 318-319 Chemistry and Mechanism of action section). 3378, paragraph 1).” From this the Examiner concludes that “it would have been obvious to one of ordinary skill in the art at the time of the instantly claimed invention to prepare a medicament using ZD6474 with any of the claimed platinum anti-cancer agents, cisplatin or carboplatin or oxaliplatin thus resulting in the practice of the instantly claimed invention (Claims 7-9) with a reasonable expectation or success.”

First of all, while the Examiner correctly acknowledges that Hennequin ‘651 fails to teach the use of oxaliplatin with ZD6474, the Examiner is reminded of the acknowledgement at the top of page 6 of the Action that “Hennequin does not however teach the specific use of ZD6474 with platinum derivatives.” The Examiner asserted that this deficiency in Hennequin ‘651 is cured by teachings of Kuenen, which assertion it is believed was sufficiently refuted

above. The Examiner is referred to Applicants' above arguments with respect to the teachings of Hennequin WO '651 and Kuenen for their response to the present obviousness ground for rejection as well.

As discussed further below, the Desoize reference also does not overcome this deficiency in Hennequin '651 with respect to the specific use of ZD6474 with platinum derivatives. It is therefore not seen how Desoize, which is a general review of platinum compounds making no reference to combinations with ZD6474 (nor any VEGF inhibitor, for that matter), can said to render method of treatment claims 14, 15 and/or 16 obvious, where these claims are directed toward the method of treatment of claims 12 and 13 wherein the platinum anti-tumour agent in the combined therapy with ZD6474 is more specifically recited as being cisplatin, carboplatin and oxaliplatin, respectively.

Desoize is a general review of platinum compounds and teaches very little in relation to combinations. In section 5.3 third paragraph the combination of carboplatin and paclitaxel is mentioned and in section 5.4 2nd paragraph the combination of oxaliplatin with leucovorin and fluorouracil is mentioned. However, these are the only mentions in the paper of combinations and there is no teaching to suggest other combinations should be tried let alone teaching as to other specific combinations which should be tested. Since Desoize does not address the acknowledged deficiency of Hennequin WO '651 with regard to the specific use of ZD6474 with platinum derivatives, no reason can be seen why the skilled person would be motivated to combine the teachings of Desoize with Hennequin WO '651. Moreover, if *all* of the art is considered in context (which it must be), the disclosure of Kuenen, as discussed above, would if anything *teach away* from combining ZD6474 with cisplatin, and if Desoize is applied as the Examiner suggests, would also teach against combining ZD6474 with carboplatin and oxaliplatin.

The Examiner does not specifically state in context of this rejection (pages 7-8 of the Action) how the third reference (Gorski) is applied. Nevertheless, Applicants refer the Examiner to their comments on Gorski in relation to the first obviousness rejection discussed above. In particular, Applicants again point out that Gorski does not even address (no less cure) the deficiency of Hennequin '651 with regard to the specific use of ZD6474 with platinum derivatives.

Accordingly, it is respectfully submitted that this second obviousness ground for rejection does not give rise to *prima facie* obviousness of any of the claims, but even if *prima facie* obviousness was asserted to be established, it has been overcome for the same reasons detailed above with respect to the first obviousness ground for rejection. It is therefore respectfully requested that this second obviousness ground for rejection be withdrawn.

***Listing of Technically Related Pending Applications of Applicants' Assignee***

The Examiner's attention is called to the following Table of technically related pending U.S. applications of Applicants' assignee, each of which claims a combination of ZD6474 with another therapeutic agent identified under the heading "Combination." The current status of each application as reported in the PAIR database is given in the right-hand column. Each of the published US applications and PCT applications is listed on a form PTO-1449 attached to an Information Disclosure Statement being submitted herewith, and a copy of each listed published PCT application is provided with the Information Disclosure Statement.

It is assumed that the Examiner has ready electronic access to each of the pending US applications, but the undersigned will provide a copy of any document from these files if requested by the Examiner.

US Appl No.	Date US Filed	US Pub #	PCT Pub #	Combination	Current Status
10/240413	01-Oct- 2002	US 2003-0144298	WO2001/74360	Anti-hypertensive	Pending before Examiner Rae, GAU 1611; Response to non-final rejection filed July 2, 2008
10/494704	19-Oct-2004	US 2005-0043395	WO2003/039551	Taxane	Pending before Examiner Pagonaksis, GAU 1614; Final rejection mailed August 25, 2008
10/543106	22-Jul-2005	US 2006-0142316	WO2004/071397	5-FU/CPT-11	Pending before Examiner Stone, GAU 1614; Final rejection mailed July 23, 2008
10/523832	08-Feb-2005	US 2005-0222183	WO2004/014383	radiotherapy	Pending before Examiner Stone, GAU 1614; Final rejection mailed July 11, 2008
10/523838	08-Feb-2005	US 2005-0245549	WO2004/014426	Iressa (ZD1839)	Pending before Examiner Stone, GAU 1614; Final rejection mailed July 10, 2008
10/530567	07-Apr-2005	US 2006-0009418A1	WO2004/032937	Gemcitabine	Pending before Examiner Finn, GAU 1614; Response to non-final rejection filed June 4, 2008

US Appl No.	Date US Filed	US Pub #	PCT Pub #	Combination	Current Status
11/663913	27-Mar-2007	US 2008-0119479	WO2006/035204	Imatinib	Pending before Examiner Pagonaksis, GAU 1614; Restriction requirement mailed September 8, 2008
11/666762	12-Dec-2007	US 2008-0200436	WO2006/048633	Anti-androgen	Pending before Examiner Pagonaksis, GAU 1614; Restriction requirement mailed September 5, 2008
12/158264	19-Jun-2008	--	WO2007/071958	pemetrexed	Pending before Examiner Pagonaksis, GAU 1614; Predicted first Action 39 months

The Examiner's Attention is also called to the following Table of technically related pending U.S. applications of Applicants' assignee, each of which claims a combination of a platinum anti-tumour agent with another therapeutic agent identified under the heading "Combination." The current status of this application as reported in the PAIR database is given in the right-hand column. The published US applications and PCT application are listed on the form PTO-1449 attached to the Information Disclosure Statement being submitted herewith, and a copy of the listed published PCT application is provided with the Information Disclosure Statement.

Again, it is assumed that the Examiner has ready electronic access to this pending US application, but the undersigned will provide a copy of any document from these files if requested by the Examiner.

US Appl No.	Date US Filed	US Pub #	PCT Pub #	Combination	Current Status
10/594,235	25-Sep-2006	US 2008-0113039	WO 2005/092384	AZD2171	Assigned to Examiner Shyam Nathan in GAU 4161; restriction mailed 17-Jul-2008

Finally, the Examiner's attention is drawn to US 7,173,038 which corresponds to Hennequin WO '651 (previously cited) applied and discussed above; and to continuing application 11/642,979 pending before Examiner Truong in GAU 1624, with a predicted first action in 6 months, which published as US 2007-0265286-A1. Again, this issued patent and

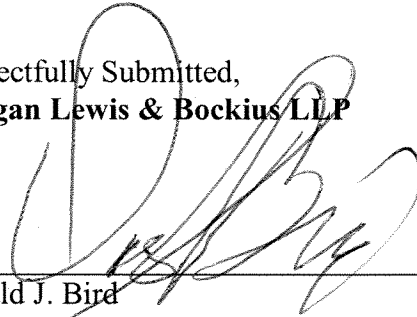
US published application are listed on the form PTO-1449 attached to the Information Disclosure Statement being submitted herewith, it is assumed that the Examiner has ready electronic access to this pending US application, but the undersigned will provide any copy from this file if requested by the Examiner.

***Conclusion***

All ground for objection and/or rejection having been addressed and, it is believed, overcome by the above amendments and/or arguments, all claims should now in condition for allowance, and a Notice to that effect is respectfully requested.

**EXCEPT** for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,  
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